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CLINICAL REPORT

Long-term Treatment with 0.1% Tacrolimus Ointment in Adults with Atopic Dermatitis: Results of a Two-year, Multicentre, Non-comparative Study

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Atopic dermatitis often requires long-term treatment. This European, multicentre, non-comparative, 24-month, follow-up study investigated the efficacy and safety of 0.1% tacrolimus ointment applied to adults with atopic dermatitis. Patients (*n*=672) applied a thin layer of 0.1% tacrolimus ointment twice daily for 3 weeks to all affected body areas. After 3 weeks, ointment was applied once daily. Clinical improvement became apparent after 2 weeks of treatment and 65.5% of patients had a rating of clearance, excellent or marked improvement by month 3. Skin burning (31.7%) was the most common causally-related adverse event, followed by pruritus (11.3%) folliculitis (6.4%), alcohol intolerance (5.7%), herpes simplex (5.7%), skin infection (4.6%), skin erythema (3.3%) and hyperaesthesia (2.4%). The most commonly reported infections were flu syndrome (12.9%), skin infection (9.8%), folliculitis (7.4%) and herpes simplex (7.0%). Long-term treatment up to 24 months with 0.1% tacrolimus ointment is safe and efficacious in adults with atopic dermatitis. *Key words: atopic dermatitis; long-term treatment; tacrolimus ointment.*

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Atopic dermatitis (AD) tends to be a chronic disease with a relapsing course. Long-term treatment is usually necessary to control and prevent flares, and patients require medication that is safe and efficacious when applied continuously or intermittently over a prolonged period of time. Tacrolimus ointment was developed specifically for the treatment of AD, and the twice daily application of 0.1% tacrolimus ointment has proven to be effective in improving the clinical condition of adults with moderate to severe AD (1–3). However following reports of lymphoma and skin cancer in children and adults applying topical calcineurin inhibitors, such as tacrolimus and pimecrolimus, in April 2005 the European Agency for the Evaluation of Medicinal Products (EMEA) started a safety review of tacrolimus and pimecrolimus in the treatment of AD (4).

The main concern of the health authorities is not that topical calcineurin inhibitors have a direct carcinogenic effect, but rather that they cause systemic immunosuppression, thus enabling the progression of malignancy. Studies investigating the systemic absorption of tacrolimus ointment have reported that absorption is minimal in most patients and there is no evidence of cumulative immunosuppression (5, 6). High blood levels of tacrolimus have been observed only in patients who have a severely impaired epidermal barrier (7) and tacrolimus ointment is contra-indicated for such patients.

The effect of topical calcineurin inhibitors on the immune system has been investigated in vaccination studies. The seropositivity rates for tetanus, diphtheria, measles or rubella in children with AD following vaccination were found to be unaffected after 2 years of treatment with 1% pimecrolimus cream (8). In addition, it was shown recently that 0.03% tacrolimus ointment had no effect on the immediate response to vaccination, the generation of immune memory, or humoral and cell-mediated immunity in children with moderate to severe AD vaccinated against meningococcal serogroup C (9). Investigating the outcome of long-term treatment with calcineurin inhibitors, Koo et al. (10) treated 7923 patients for up to 23 months with 0.03% or 0.1% tacrolimus ointment and found no increase in the incidence of infections or other adverse events. In an open-label study, Hanifin et al. (11) followed up 300 patients who applied 0.1% tacrolimus ointment either continuously or intermittently for 4 years. The authors noted no increase in the incidence of cutaneous infections with long-term treatment, and the incidence rates of varicella zoster (chicken pox and shingles) and flu-like symptoms were comparable with the expected rates in the general population.

A definite link between topical calcineurin inhibitors and cancer has not been established. In March 2006,

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the EMEA concluded, following its review, that the benefits of using tacrolimus and pimecrolimus outweigh the risks, but more long-term safety data are required accurately to assess any risk to patients using these treatments. Here we report the first long-term data from a European multicentre, open-label, follow-up study that investigated the efficacy and safety of 0.1% tacrolimus ointment applied for up to 24 months to adults with AD.

METHODS

Study design

This was a 24-month, multicentre, non-comparative, phase III/IV, follow-up study conducted in 52 centres in 12 European countries. All study centres that had previously contributed to the 6-month comparative study, i.e. 0.1% tacrolimus ointment vs. corticosteroid ointment regimen (1) were invited to participate. The study was conducted in accordance with the ethical principles described in the Declaration of Helsinki, and the Ethics Committee of each centre reviewed the protocol and granted approval before the start of the study. Patients were to remain in the study until the next scheduled visit following product launch. Assessments were performed on day 1, week 2, month 1, month 3 and 3-monthly thereafter.

Patients

Following written informed consent from the patient, male and female patients aged 18 years or older with a diagnosis of AD based on the criteria of Hanifin & Rajka (12) were enrolled in the study.

Method of assigning patients to the treatment group

A unique number was allocated to each patient as he or she entered the follow-up study. A gap of at least 3 days was ensured between the last application of study medication in the 6-month study and the first application of 0.1% tacrolimus ointment in this study.

Treatment

Patients applied a thin layer of 0.1% tacrolimus ointment twice daily for 3 weeks to all affected body areas. Up to 100% of the body surface area (BSA) could be treated until the lesions cleared (i.e. stopped itching). After 3 weeks, the patients applied tacrolimus ointment once daily until clearance. Patients were required to mark in their diary whether ointment was applied each day and, if so, whether one or two applications were made. In the event of flare or a worsening of the clinical condition, twice daily ointment application resumed for another 3 weeks and the change in application regimen was recorded in the patient diary. All of the used and unused ointment tubes for each patient were weighed at the end of the study so that total ointment usage could be calculated.

Therapies that were prohibited during the study included topical corticosteroids for the treatment of AD, systemic corticosteroids, ultraviolet radiation treatments, and systemic non-steroidal immunosuppressive agents. The wash-out phase for these therapies ranged from a minimum of 3 days (for topical corticosteroids and systemic corticosteroids) to a maximum of 6 weeks (for ultraviolet (UV) treatments) prior to the start of the study. The wash-out period for systemic non-steroidal immunosuppressants was 2 weeks. Patients were allowed to use a non-medicated emollient 2 hours before and after tacrolimus ointment application.

Assessments

Efficacy end-points included the physician's global evaluation of clinical response, physician's evaluation of clinical response on head and neck, physician's assessment of individual signs, affected area assessment, patient's assessment of global response, patient's assessment of global response for head and neck, and the Eczema Area and Severity Index (EASI; 13). Full details of these assessments are described in the 6-month study publication (1). Patient quality of life was measured using the disease-specific Dermatology Life Quality Index (DLQI). Safety assessments during the study included the monitoring of adverse events and vital signs, as well as clinical laboratory evaluations (haematology and clinical chemistry, including measurements of hepatic and renal function). An adverse event was defined as any untoward occurrence in a patient during the study, regardless of whether it was related to the study treatment.

Statistical methodology

The sample size for this study was not based on statistical assumptions. As this study was a follow-up of the 6-month study, the sample size was limited by the number of patients who participated in the original study. The duration of the study varied among patients and, for this reason, the last observation carried forward LOCF rule was applied for month 6, month 12, month 18, month 24 and end of study visits. The intent-to-treat population was used for all of the analyses and included all patients who received at least one application of study ointment. No statistical tests were performed.

RESULTS

Patient demographics and baseline data

In total, 672 patients formed the intent-to-treat population. Patient demographics and baseline characteristics of the study population are shown in Table I.

Patient disposition

A total of 185 patients (27.5%) discontinued the study, the most common reason for discontinuation being lack of efficacy (71 patients, 10.6%). Lost to follow-up (45, 6.7%), withdrawal of consent (23, 3.4%), adverse event (17, 2.5%) and non-compliance (14, 2.1%) were also reasons for study discontinuation. Except for the UK, where the patients participated in the study for a fixed period of 6 months, the patients remained in the study until the next scheduled visit following product launch in the respective country. Consequently, the majority of patients (338, 69.5%) completed the study between months 4 and 12, while 114 patients (23.4%) continued to apply ointment between months 13 and 24.

Ointment usage

Of the 640 patients who returned their diaries, 619 applied tacrolimus ointment once daily at least once during the study, while 624 patients applied ointment twice daily at least once during the study. The overall median percentage of treatment days was 69.9% of the study duration when taking into account days with missing information as non-treatment days, and 83.6%

Table I. *Patient demographics and baseline characteristics (n=672)*[a]

Characteristics	Value
Age (years)	
Mean ± SD	33.5 ± 11.8
Median (min–max)	31 (18–85)
Male: female, *n* (%)	329 (49.0): 343 (51.0)
Ethnic group, *n* (%)	
Caucasian	648 (96.4)
Black	7 (1.0)
Oriental	7 (1.0)
Other	10 (1.5)
Severity of AD on day 1, *n* (%)	
None	2 (0.3)
Mild	55 (8.2)
Moderate	440 (65.5)
Severe	175 (26.0)
Total affected BSA[b], day 1	
Mean±SD	23.5±22.0
Median (min–max)	16.0 (0–99.5)
Total affected BSA, day 1, *n* (%)	
0 to ≤25%	441 (65.6)
>25% to ≤50%	136 (20.2)
>50% to ≤75%	69 (10.3)
>75% to ≤100%	26 (3.9)
Affected body region (day 1), *n* (%)	
Head and neck	580 (86.3)
Upper limbs	636 (94.6)
Trunk	524 (78.0)
Lower limbs	512 (76.2)
Percentage affected BSA, (day 1) Median (min–max)	
Head and neck	25 (0–100)
Upper limbs	20 (0–100)
Trunk	15 (0–100)
Lower limbs	10 (0–100)

[a]Intent-to-treat population.
[b]Affected BSA as a percentage of total BSA.
SD: standard deviation; AD: atopic dermatitis; BSA: body surface area.

when considering days with missing information as treatment days. The median number of treatment episodes per patient was 1.0 and the median duration of treatment episodes was 45 days (Table II).

The median tacrolimus ointment use per day between day 1 and month 3 was 1.2 g, decreasing to 0.7 g between months 10–12, and 0.5 g by months 22–24. Total median ointment used during the entire study was 1.0 g/day.

Efficacy outcomes

Clinical improvement was observed after 2 weeks of treatment and the results for EASI and affected body surface area showed that most patients experienced considerable improvement in the signs and symptoms of their AD. Median EASI decreased from 8.4 on day 1 to 0.4 by month 24, while the median percentage affected total BSA decreased from 16.0 to 1.5, respectively (Figs. 1 and 2). The ratings of the physician's global evaluation of clinical response reflected the clinical improvement as measured by EASI, with 30.4% of patients receiving a rating of cleared or excellent improvement at week 2 and 43.8% of patients by month 3

Table II. *Number and duration of treatment episodes*[a]

	0.1% tacrolimus (*n* = 672)[b]	
	Assuming days with missing information as	
	Not treated	Treated
No. of treatment episodes[c]/patient		
Number of patients	640	640
Mean±SD	1.7±1.3	1.8±1.3
Median (min–max), *n* (%)	1 (0–8)	1 (0–8)
Duration of treatment episodes (days)		
Total number of episodes	1114	1147
Mean±SD	85.5±104.1	97.2±115.5
Median (min–max), *n* (%)	45 (7–799)	51 (7–799)

[a]Based on diary data, excluding 32 patients who did not return their diaries. An episode is defined as at least 7 days of treatment in a row. If in the following 3 weeks (after the last 7-day treatment period) there are another at least 7 days of consecutive treatment, then the episode is extended to the last day of that subsequent treatment period.
[b]Intent-to-treat population. SD: standard deviation.
[c]One patient may have more than one treatment episode.

(Table III). Patients were also extremely satisfied with their improvement and at week 2, 70.5% of patients assessed their overall response as much better or better. Separate analyses of the head and neck area showed overall results similar to the analyses of combined body regions: 37.3% of the patients received a rating of cleared or excellent after 2 weeks of treatment, while 73.9% of the patients assessed their head/neck area to be much better or better. Patients reported a progressive improvement in quality of life throughout the study. At the day 1 visit, the median DLQI was 6.0, and decreased to 3.0 by month 3 and 1.5 by month 24.

Safety outcomes

A total of 366 patients (54.5%) experienced adverse events that were assessed by the study investigators to be related to the study ointment. Skin burning (213 patients, 31.7%) and pruritus (76, 11.3%) were the most common causally-related adverse events and occurred

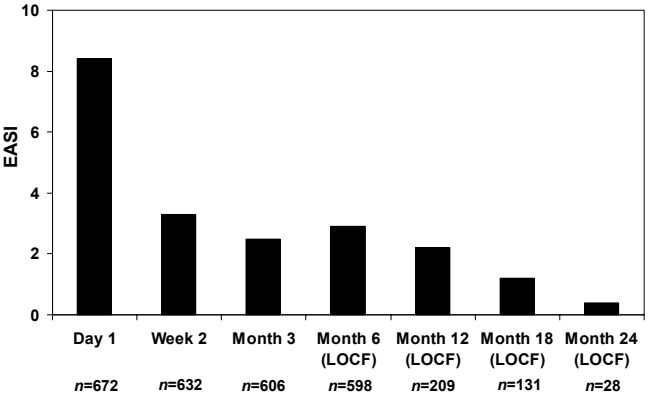

Fig. 1. Median Eczema Area and Severity Index (EASI) between visit at day 1 and month 24. LOCF: Last Observation Carried Forward.

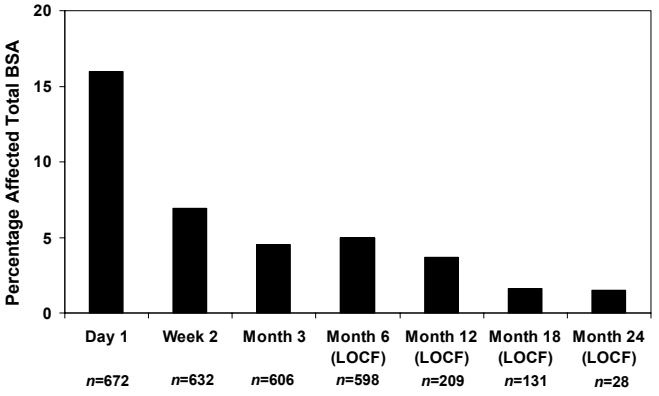

Fig. 2. Median percentage affected total body surface area (BSA) between visit at day 1 and month 24. LOCF: Last Observation Carried Forward.

most often at the site of ointment application (Table IV). In 80% of patients, skin burning and pruritus were assessed as being mild to moderate in severity, and after 2 weeks of treatment, the prevalence of both side-effects decreased greatly. Of the 17 patients (2.5%) applying tacrolimus ointment who discontinued the study because of adverse events, skin burning (8 patients) was the most common reason for premature study discontinuation. Other adverse events leading to study discontinuation included herpes simplex (2 patients), folliculitis, pruritus, eczema, skin infection, manic depressive reaction, application-site reaction and hypertension (all 1 patient, respectively).

Few serious adverse events occurred during the study (28 patients, 4.2%). The most commonly reported serious adverse event was lack of drug effect (7, 1.0%) followed by accidental injury (4, 0.6%). Four patients (0.6%) experienced a serious adverse event that was assessed as being related to treatment: one patient with severe eczema herpeticum at the sites of ointment application on the head/neck and upper limbs on day 228, one patient with severe erythrodermic eczema at both treated and untreated sites all over the body on day 29, and 2 patients with exacerbation of AD (days 61 and 78). Tacrolimus ointment application was discontinued in all 4 patients.

Reports of infections, benign neoplasms and malignancies were examined carefully. The most commonly reported infections during this study were flu syndrome (12.9%), skin infection (9.8%), folliculitis (7.4%) and herpes simplex (7.0%; Table V). With regard to herpes simplex, except for 6 patients (0.9%) who had severe herpes simplex that required medical intervention, all other cases of herpes simplex were mild to moderate in severity. In addition, the prevalence of herpes simplex decreased throughout the study period in parallel with the decrease in severity and extent of disease as the skin barrier function improved (Fig. 3). Two malignancies were reported during the study, and in both patients the relationship to tacrolimus ointment was assessed as being unlikely. Bowen's disease was diagnosed in a 58-year-old man on day 245, (the patient continued with the study ointment and recovered) and a prostate cancer was identified in an 82-year-old patient on day 119.

With respect to the 7 patients with benign skin neoplasms, 5 had neoplasms that were assessed by the physician as having an unlikely relationship to the study ointment (each one patient: seborrhoeic wart, strange coloured mole, junctional nevus, molluscum pendulum, inflammatory sebaceous cyst). Two patients had benign skin neoplasms that were possibly related to the study medication (one patient with a wart and one patient with neck skin tags). All 7 patients continued with tacrolimus ointment application and recovered prior to the end of the study.

Twenty-seven patients had at least one laboratory value that occurred during the study that was considered

Table III. *Clinical improvement in atopic dermatitis between day 1 and end of study*

	0.1% tacrolimus (n = 672)	
	N	*n* (%)
Physician's Global Evaluation of Clinical Response		
Cleared or excellent improvement		
Week 2	628	191 (30.4)
Month 3	605	265 (43.8)
End of study (LOCF)	664	270 (40.7)
Head/Neck		
Cleared or excellent improvement		
Week 2	553	206 (37.3)
Month 3	533	288 (54.0)
End of study (LOCF)	590	271 (45.9)
Patient's Assessment of Global Response		
Much better or better	631	445 (70.5)
Week 2	603	455 (75.5)
Month 3	665	476 (71.6)
End of study (LOCF)		
Head/Neck		
Much better or better		
Week 2	590	436 (73.9)
Month 3	567	441 (77.8)
End of study (LOCF)	642	465 (72.4)

Intent-to-treat population.
LOCF: Last Observation Carried Forward; N: total number of patients.

Table IV. Incidence of most common[a] causally related adverse events during 0.1% tacrolimus therapy (n=672)[b]

COSTART[c] term	*n* (%)
Skin burning	213 (31.7)
Pruritus	76 (11.3)
Folliculitis	43 (6.4)
Alcohol intolerance	38 (5.7)
Herpes simplex	38 (5.7)
Skin infection	31 (4.6)
Lack of drug effect	22 (3.3)
Skin erythema	22 (3.3)

[a]At least 2% of patients.
[b]Intent-to-treat population.
[c]Food and Drug Administration's (FDA) Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART).

Table V. *Overall incidence of most common[a] infections and incidence of all benign neoplasms and malignancies, irrespective of causality, during 0.1% tacrolimus therapy (n=672)[b]*

COSTART[c] term	*n* (%)
Infections	
Flu syndrome	87 (12.9)
Skin infection	66 (9.8)
Folliculitis	50 (7.4)
Herpes simplex	47 (7.0)
Infection	24 (3.6)
Pharyngitis	22 (3.3)
Gastroenteritis	15 (2.2)
Malignancies	
Skin neoplasm benign	7 (1.0)
Prostatic carcinoma	1 (0.1)
Skin cancer	1 (0.1)

[a]At least 2% of patients.
[b]Intent-to-treat population.
[c]Food and Drug Administration's (FDA) Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART).

to be clinically relevant by the investigator. None of these clinically-relevant laboratory values affected the management of the patient or led to discontinuation of the patient from the study.

DISCUSSION

This is the first European study to investigate the long-term efficacy and safety of 0.1% tacrolimus ointment applied either continuously or intermittently for up to 24 months to adults with AD. The efficacy data showed clearly that the patients had substantial improvement in the signs and symptoms of AD. Large decreases in total affected BSA and EASI became apparent after 2 weeks of treatment and clinical improvement continued throughout the study. The positive results of the DLQI showed that patients had a greater feeling of well-being and felt that their lives were less impaired by their disease. Treatment efficacy was maintained in the majority of patients who required only one to two treatment episodes during the study period, and the total amount of ointment applied decreased as the condition of the skin improved. This is of particular importance as there is concern that patients who have large affected areas and open lesions may be at a risk of increasing their systemic exposure to tacrolimus. Rubins et al. (6) found that in 32 adults with moderate to severe AD, 96% of the blood samples assayed contained tacrolimus concentrations below 1 ng/ml and 23% of the samples were below the lower limit of quantification (0.025 ng/ml. As treatment with tacrolimus ointment normally helps to restore the skin barrier quickly, exposure to tacrolimus is reduced as the lesions heal. In a 12-month, open-label study in 316 patients with moderate to severe AD, tacrolimus whole blood concentrations decreased from 0.32 ng/ml at week 1 to 0.13 ng/ml at month 12 (14). Nonetheless, patients should be monitored carefully to identify any side-effects related to long-term treatment, and additional studies measuring whole blood concentrations of tacrolimus in patients applying tacrolimus ointment for prolonged periods of time will help clarify whether systemic accumulation can occur with long-term treatment.

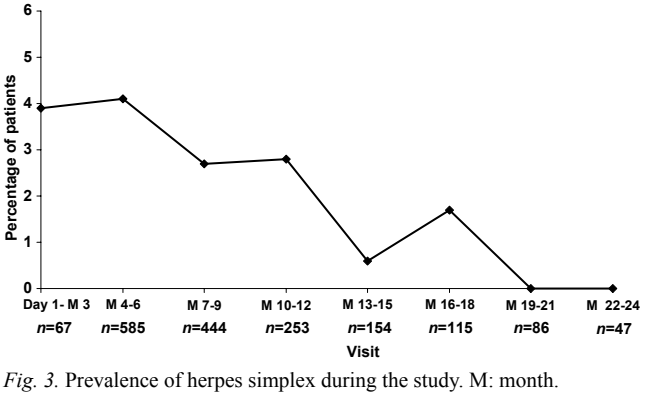

Fig. 3. Prevalence of herpes simplex during the study. M: month.

Irritation at the site of ointment application is the most common adverse effect associated with tacrolimus ointment and has been reported in both short-term and long-term clinical studies (15). Transient skin burning at the site of ointment application was the most common adverse event reported during our study, and in most patients, was mild to moderate in severity, decreased in prevalence after the first 2 weeks of treatment, and only a few patients required medical intervention. As there is concern that the prolonged application of tacrolimus ointment may cause systemic immunosuppression, we investigated infections and malignancies in detail. The nature and incidence of infections observed during the study were consistent with what has been reported previously in a cohort of patients with AD followed for this length of time (11). With regard to cutaneous infections, the overall incidence of herpes simplex in the patients in our study was 7%, which is in agreement with reported incidence rates in patients with AD of 6–10% (16, 17). Only one patient (0.1%) developed eczema herpeticum, which is a very low incidence compared with previous reports (18). Our data are in agreement with those of Fleischer et al. (19) who analysed the data for 1554 patients with AD treated with tacrolimus ointment in five clinical trials for time periods ranging between 12 weeks and up to 12 months. They found that the risk of cutaneous bacterial, viral, or fungal infections did not increase with long-term treatment. Importantly in our study, the prevalence of herpes simplex decreased over time despite patients with AD often having a high risk of recurrent herpes simplex infections (20), and it is possible that the clinical efficacy of tacrolimus ointment in improving the epidermal barrier may decrease the risk of local infection.

We observed only 2 malignancies (Bowens disease and prostate cancer) that occurred during the study,

both of which were considered to be unrelated to the study ointment. In other clinical studies of tacrolimus ointment, there has been no evidence of an increased risk of lymphoma, lymphoproliferative disorders, or skin cancers associated with the use of tacrolimus ointment (14, 22). The overall rate of lymphoma in the US general population is 22/100 000 person years and it has been reported that the overall rate in tacrolimus-treated patients is 0.65/100 000 (23). With regard to skin cancer, Naylor et al. (24) studied the data of 9813 adult and pediatric patients with moderate to severe AD who applied 0.03% or 0.1% tacrolimus ointment twice daily. The patients were evaluated every 3 months, with the mean duration of observation being 208 days and the longest period of observation 1479 days. Thirteen patients of 4761 adult patients with AD (0.27%) were diagnosed with unrelated non-melanoma skin cancer, and the authors concluded that there was no increased risk of non-melanoma skin cancer in patients applying tacrolimus ointment compared with the general US population.

Topical calcineurin inhibitors have only been available for the last 5–6 years, but already there have been more than 5.4 million prescriptions of tacrolimus ointment worldwide (23). Although more information is required regarding long-term outcome with tacrolimus ointment, the long-term safety data currently available are encouraging. The results of this 24-month study confirm that the application of 0.1% tacrolimus ointment, either continuously or intermittently, is efficacious in reducing the signs and symptoms of AD in adults, and that treatment efficacy can be maintained successfully. The safety profile observed in our patients is consistent with previous reports, and no increase in infection, malignancy, or other cumulative side-effects were noted following the prolonged application of tacrolimus ointment. In conclusion, tacrolimus ointment has an invaluable role in the challenging management of AD, and additional long-term, follow-up studies will help to address and further elucidate the safety profile of long-term tacrolimus ointment treatment.

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